

## SEQUENCE LISTING

## <110> Astra Aktiebolag

<120> Vaccine Delivery System and Method of Production

<130> 1103326-0560

<140> 09/308,435

<141> 1999-05-19

<150> PCT/SE99/00582

<151> 1999-04-09

<150> SE 9801288-3

<151> 1998-04-14

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<170> PatentIn Ver. 2.1

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|     |      |       |       |       |       |       |       |       |      | gac<br>Asp        |     | _     | -     |       | _                | 1263 |

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Lys Val Ile Ser Val Asp Ser Ser Asp Lys Asp Asp Phe Ser Phe Ala 100 105 110

Gln Lys Lys Glu Gly Tyr Leu Ala Val Ala Met Asn Gly Glu Ile Val 115 120 125

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180 185 190

Phe Leu Lys Thr Thr His Ser Ser His Ser Gly Gly Leu Val Ser Thr 195 200 205

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Pro Ala Ser Glu Lys Val Gln Ala Leu Asp Glu Lys Ile Leu Leu Leu

55

975

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|   |   |   |   |   |   |   |   | tat<br>Tyr        |   |   |   |   |   |   |   | 1167 |
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|   |   |   |   |   |   |   |   | tct<br>Ser        |   |   |   |   | - |   | _ | 1551 |

|            | aaa<br>Lys<br>255               |            |            | _         |            |            | taaa       | aaaca      | aaa       | taac       | gcata      | aa ga      | aaaa       | gaac      | Đ          | 1602 |
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| Leu        | Gly                             | Ala        | Ser<br>20  | Val       | Val        | Ala        | Leu        | Leu<br>25  | Val       | Gly        | Cys        | Ser        | Pro<br>30  | His       | Ile        |      |
| Ile        | Glu                             | Thr<br>35  | Asn        | Glu       | Val        | Ala        | Leu<br>40  | Lys        | Leu       | Asn        | Tyr        | His<br>45  | Pro        | Ala       | Ser        |      |
| Glu        | Lys<br>50                       | Val        | Gln        | Ala       | Leu        | Asp<br>55  | Glu        | Lys        | Ile       | Leu        | Leu<br>60  | Leu        | Arg        | Pro       | Ala        |      |
| Phe<br>65  | Gln                             | Туr        | Ser        | Asp       | Asn<br>70  | Ile        | Ala        | Lys        | Glu       | туr<br>75  | Glu        | Asn        | Lys        | Phe       | Lys<br>80  |      |
| Asn<br>,   | Gln                             | Thr        | Ala        | Leu<br>85 | Lys        | Val        | Glu        | Gln        | Ile<br>90 | Leu        | Gln        | Asn        | Gln        | Gly<br>95 | Tyr        |      |
| Lys        | Val                             | Ile        | Ser<br>100 | Val       | Asp        | Ser        | Ser        | Asp<br>105 | Lys       | Asp        | Asp        | Phe        | Ser<br>110 | Phe       | Ala        |      |
| Gln        | Lys                             | Lys<br>115 | Glu        | Gly       | Tyr        | Leu        | Ala<br>120 | Val        | Ala       | Met        | Asn        | Gly<br>125 | Glu        | Ile       | Val        |      |
| Leu        | Arg<br>130                      | Pro        | Asp        | Pro       | Lys        | Arg<br>135 | Thr        | Ile        | Gln       | Lys        | Lys<br>140 | Ser        | Glu        | Pro       | Gly        |      |
| Leu<br>145 | Leu                             | Phe        | Ser        | Thr       | Gly<br>150 | Leu        | Asp        | Lys        | Met       | Glu<br>155 | Gly        | Val        | Leu        | Ile       | Pro<br>160 |      |
| Ala        | Gly                             | Phe        | Ile        | Lys       | Val        | Thr        | Ile        | Leu        | Glu       | Pro        | Met        | Ser        | Gly        | Glu       | Ser        |      |

Leu Asp Ser Phe Thr Met Asp Leu Ser Glu Leu Asp Ile Gln Glu Lys 180 185 Phe Leu Lys Thr Thr His Ser Ser His Ser Gly Gly Leu Val Ser Thr 200 Met Val Lys Gly Thr Asp Asn Ser Asn Asp Ala Ile Lys Arg Ala Leu 215 220 Asn Lys Ile Phe Ala Asn Ile Met Gln Glu Ile Asp Lys Leu Thr 225 230 Gln Lys Asn Leu Glu Ser Tyr Gln Lys Asp Ala Lys Glu Leu Lys Gly 245 250 Lys Arg Asn Arg 260 <210> 5 <211> 60 <212> PRT <213> Helicobacter pylori Met Lys Thr Asn Gly His Phe Lys Asp Phe Ala Trp Lys Lys Cys Leu 5 10 15 Leu Gly Thr Ser Val Val Ala Leu Leu Val Gly Cys Ser Pro His Ile 20 25 30 Ile Glu Thr Asn Glu Val Ala Leu Lys Leu Asn Tyr His Pro Ala Ser 35 40 Glu Lys Val Gln Ala Leu Asp Glu Lys Ile Leu Leu 50 55 60 <210> 6 <211> 60 <212> PRT <213> Helicobacter pylori <400> 6

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<220>

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<223> n-propyl alcohol attached to sulfhydryl group of cysteine residue at position 31

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1 5 10 15

Leu Gly Ala Ser Val Val Ala Leu Leu Val Gly Leu Ala Gly Cys
20 25 30

<210> 25

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<222> (31)

<223> lipid chains a and b attached respectively at positions 3 and 2 of propyl group attached to sulfhydryl of cysteine residue at position 31

<400> 25

Met Arg Ala Asn Asn His Phe Lys Asp Phe Ala Trp Lys Lys Cys Leu 1 5 10 15

Leu Gly Ala Ser Val Val Ala Leu Leu Val Gly Leu Ala Gly Cys 20 25 30

5

10

15



22

(1993) J. Bacteriol. 175, 674-683. Reference is also made to P W Toole et al, Bacteriology Vol. 177, No. 21, Nov. 1995; and Jones, A.C., Logan, R.P., Foynes, S., Cockayne, A., Wren, B.W. and Penn, C.W., J. Bacteriol. 179 (17), 5643-5647 (1997) which concern HpaA proteins.

The Hpa A protein is expressed by all *H. pylori* strains tested, and antibodies created towards this protein do not cross-react with common endogenous human bacteria of other species or with selected human tissues including the gastric mucosa. Thus being a well conserved putative adhesin with immunogenic properties, the HpaA protein is useful both for the detection of *H. pylori* infections as well as for the manufacture of vaccine compositions. Table 1 shows a comparison of HpaA amino acid sequences derived from 4 different strains of *H. Pylori*. It can be seen from the table that the sequence is highly conserved amongst different strains.

## Table 1

|    | Evans (8826)  | MKTNGHFKDFAWKKCLLGTSVVALLVGCSPHIIETNEVALKLNYHPASEKVQALDEKILL (SEQ ID NO:5)  |
|----|---------------|---|
|    | GTC (J99)     | MKTNGHFKDFAWKKCFLGASVVALLVGCSPHIIETNEVALKLNYHPASEKVQALDEKILL (SEQ ID NO:6)  |
|    | Trust (17874) | MKTNGHFKDFAWKKCLLGASVGALLVGCSPHIIETNEVALKLNYHPASEKVQALDEKILL (SEQ ID NO:7)  |
| 20 | Penn (11637)  | MRANNHFKDFAWKKCLLGASVVALLVGCSPHIIETNEVALKLNYHPASEKVQALDEKILL (SEQ ID NO:8)  |
|    | TIGR (26695)  | MKANNHFKDFAWKKCLLGASVVALLVGCSPHIIETNEVALKLNYHPASEKVQALDEKILL (SEQ ID NO:9)  |
|    |               | *::*.*********  |
|    |               |   |
|    | Evans (8826)  | LKPAFQYSDNIAKEYENKFKNQTTLKVEEILQNQGYKVINVDSSDKDDFSFAQKKEGYLA (SEQ ID NO:10) |
| 25 | GTC (J99)     | LRPAFQYSDNĮAKEYENKFKNQTTLKVEEILQNQGYKVINVDSSDKDDFSFAQKKEGYLA (SEQ ID NO:11) |
|    | Trust (17874) | LRPAFQYSDNIAKEYENKFKNQTVLKVEQILQNQGYKVINVDSSDKDDFSFAQKKEGYLA (SEQ ID NO:12) |
|    | Penn (11637)  | LRPAFQYSDNIAKEYENKFKNQTALKVEQILQNQGYKVISVDSSDKDDFSFAQKKEGYLA (SEQ ID NO:13) |
|    | TIGR (26695)  | LRPAFQYSDNIAKEYENKFKNQTALKVEQILQNQGYKVISVDSSDKDDLSFSQKKEGYLA (SEQ ID NO:14) |
|    |               | *;*************************************                                     |

| Evans (8826)  | VAMIGEIVLRPD?KRTIQKKSEPGLLFSTGLDKMEGVLIPAGFVKVTILEPMSGESLDSF | (SEQ | TD | NO:13) |
|---------------|--|------|----|--------|
| Evallo (erra) | VAMNGEIVLRPDPKRTIQKKSEPGLLFSTGLDKMEGVLIPAGFVKVTILEPMSGESLDSF | (SEQ | ID | NO:16) |
|               | VAMNGEIVLRPDPKRTIQKKSEPGLLFSTGLDKMEGVLIPAGFVKVTILEPMSGESLDSF | (SEQ | ID | NO:16) |
|               | VAMNGEIVLRPDPKRTIQKKSEPGLLFSTGLDKMEGVLIPAGFIKVTILEPMSGESLDSF |      |    |        |
| Penn (11637)  | VAMNGEIVLRPDPKRTIQKKSEPGLLESIGLDKALEGVLIFAGEIKVIIBLIKGGDGTG  | (ODQ |    |        |

|    | TIGR (26695)  | VAMNGEIVLRPDPKRTIQKKSEPGLLFSTGLDKMEGVLIPAGFVKVTILEPMSGESLDSF (SEQ ID NO:1  | 6) |
|----|---------------|--|----|
|    |               |  |    |
|    |               |  |    |
|    | Evans (8826)  | TMDLSELDIQEKFLKTTHSSHSGGLVSTMVKGTDNSNDAIKSALNKIFASIMQEMDKKLT (SEQ ID NO:1  | 8) |
| 5  | GTC (J99)     | TMDLSELDIQEKFLKTTHSSHSGGLVSTMVKGTDNSNDAIKSALNKIFASIMQEMDKKLT (SEQ ID NO:1  | 8) |
|    | Trust (17874) | TMDLSELDIQEKFLKTTHSSHSGGLVSTMVKGTDNSNDAIKSALNKIFGSIMQEIDKKLT (SEQ ID NO:19 | 9) |
|    | Penn (11637)  | TMDLSELDIQEKFLKTTHSSHSGGLVSTMVKGTDNSNDAIKSALNKIFANIMQEIDKKLT (SEQ ID NO:20 | 0) |
|    | TIGR (26695)  | TMDLSELDIQEKFLKTTHSSHSGGLVSTMVKGTDNSNDAIKSALNKIFANIMQEIDKKLT (SEQ ID NO:2  | 0) |
|    |               | ********   |    |
| 10 |               |  |    |
|    | Evans (8826)  | QRNLESYQKDAKELKNKRNR (SEQ ID NO:21)  |    |
|    | GTC (J99)     | QRNLESYQKDAKELKNKRNR (SEQ ID NO:21)  |    |
|    | Trust (17874) | QKNLESYQKDAKELKGKRNR (SEQ ID NO:22)  |    |
|    | Penn (11637)  | QKNLESYQKDAKELKGKRNR (SEQ ID NO:22)  |    |
| 15 | TIGR (26695)  | QKNLESYQKDAKELKGKRNR (SEQ ID NO:22)  |    |
|    |               | *;*****************  |    |

"\*" at a certain position denotes an identical amino acid in all sequences

"." at a certain position denotes conserved amino acids (eg, amino acids of the same charge type such as lysine or arginine at a certain position).

| Penn (11637)  | DNA sequence deposited in Genbank under Accession No. X92502 |
|---------------|--|
| Trust (17874) | DNA sequence deposited in Genbank under Accession No.U35455  |
| Evans (8826)  | DNA sequence deposited in Genbank under Accession No.X61574  |
| TIGR (26695)  | DNA sequence deposited under Accession No. AE000591          |
| GTC (J99)     | DNA sequence obtained in-house.                              |

The strain names are indicated in brackets, strain 8826 being obtained from SWISS-PROT accession Q48264.

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(1993) J. Bacteriol. 175, 674-683. Reference is also made to P W Toole et al, Bacteriology Vol. 177, No. 21, Nov. 1995; and Jones, A.C., Logan, R.P., Foynes, S., Cockayne, A., Wren, B.W. and Penn, C.W., J. Bacteriol. 179 (17), 5643-5647 (1997) which concern HpaA proteins.

The Hpa A protein is expressed by all *H. pylori* strains tested, and antibodies created towards this protein do not cross-react with common endogenous human bacteria of other species or with selected human tissues including the gastric mucosa. Thus being a well conserved putative adhesin with immunogenic properties, the HpaA protein is useful both for the detection of *H. pylori* infections as well as for the manufacture of vaccine compositions. Table 1 shows a comparison of HpaA amino acid sequences derived from 4 different strains of *H. Pylori*. It can be seen from the table that the sequence is highly conserved amongst different strains.

## Table 1

|    | Evans (8826)  | MKTNGHFKDFAWKKCLLGTSVVALLVGCSPHIIETNEVALKLNYHPASEKVQALDEKILL (SEQ ID NO:5)  |
|----|---------------|---|
|    | GTC (J99)     | MKTNGHFKDFAWKKCFLGASVVALLVGCSPHIIETNEVALKLNYHPASEKVQALDEKILL (SEQ ID NO:6)  |
|    | Trust (17874) | MKTNGHFKDFAWKKCLLGASVGALLVGCSPHIIETNEVALKLNYHPASEKVQALDEKILL (SEQ ID NO:7)  |
| 20 | Penn (11637)  | MRANNHFKDFAWKKCLLGASVVALLVGCSPHIIETNEVALKLNYHPASEKVQALDEKILL (SEQ_ID_NO:8)  |
|    | TIGR (26695)  | MKANNHFKDFAWKKCLLGASVVALLVGCSPHIIETNEVALKLNYHPASEKVQALDEKILL (SEQ ID NO:9)  |
|    |               | *::*:*******  |
|    |               |   |
|    | Evans (8826)  | LKPAFQYSDNIAKEYENKFKNQTTLKVEEILQNQGYKVINVDSSDKDDFSFAQKKEGYLA (SEQ ID NO:10) |
| 25 | GTC (J99)     | LRPAFQYSDNIAKEYENKFKNQTTLKVEEILQNQGYKVINVDSSDKDDFSFAQKKEGYLA (SEQ ID NO:11) |
|    | Trust (17874) | LRPAFQYSDNIAKEYENKFKNQTVLKVEQILQNQGYKVINVDSSDKDDFSFAQKKEGYLA (SEQ ID NO:12) |
|    | Penn (11637)  | LRPAFQYSONIAKEYENKFKNQTALKVEQILQNQGYKVISVDSSDKDDFSFAQKKEGYLA (SEQ ID NO:13) |
|    | TIGR (26695)  | LRPAFQYSDNIAKEYENKFKNQTALKVEQILQNQGYKVISVDSSDKDDLSFSQKKEGYLA (SEQ_ID_NO:14) |
|    |               | *;*************************************                                     |

| Evans (8826) VAMIGEIVLRPDPKRTIQKKSEPGLLFSTG  | LDKMEGVLIPAGFVKVTILEPMSGESLDSF (SEQ ID NO:15)  |
|--|--|
| DATE OF THE PROPERTY OF THE PR | LDKMEGVLIPAGFVKVTILEPMSGESLDSF (SEQ ID NO:16)  |
| GIO (GIO)  | LDKMEGVLIPAGFVKVTILEPMSGESLDSF (SEQ ID NO:16)  |
|  | GLOKMEGVLIPAGFIKVTILEPMSGESLDSF (SEQ ID NO:17) |

|    | TIGR (26695)               | VAMNGEIVLRPDPKRTIQKKSEPGLLFSTGLDKMEGVLIPAGFVKVTILEPMSGESLDSF (SEQ_ID_NO:16) |
|----|----------------------------|---|
|    |                            | *** *********************************                                       |
|    |                            |   |
|    | Evans (8826)               | TMDLSELDIQEKFLKTTHSSHSGGLVSTMVKGTDNSNDAIKSALNKIFASIMQEMDKKLT (SEQ ID NO:18) |
| 5  | GTC (J99)                  | TMDLSELDIQEKFLKTTHSSHSGGLVSTMVKGTDNSNDAIKSALNKIFASIMQEMDKKLT (SEQ_ID_NO:18) |
|    | Trust (17874)              | TMDLSELDIQEKFLKTTHSSHSGGLVSTMVKGTDNSNDAIKSALNKIFGSIMQEIDKKLT (SEQ_ID_NO:19) |
|    | Penn (11637)               | TMDLSELDIQEKFLKTTHSSHSGGLVSTMVKGTDNSNDAIKSALNKIFANIMQEIDKKLT (SEQ ID NO:20) |
|    | TIGR (26695)               | TMDLSELDIQEKFLKTTHSSHSGGLVSTMVKGTDNSNDAIKSALNKIFANIMQEIDKKLT (SEQ_ID_NO:20) |
|    |                            | *************   |
| 10 |                            |   |
|    | Evans (8826)               | QRNLESYQKDAKELKNKRNR (SEQ ID NO:21)   |
|    | GTC (J99)                  | QRNLESYQKDAKELKNKRNR (SEQ ID NO:21)   |
|    |                            |   |
|    | Trust (17874)              | QKNLESYQKDAKELKGKRNR (SEQ ID NO:22)   |
|    | Trust (17874) Penn (11637) | QKNLESYQKDAKELKGKRNR (SEQ ID NO:22)  QKNLESYQKDAKELKGKRNR (SEQ ID NO:22)    |
| 15 |                            |   |

"\*" at a certain position denotes an identical amino acid in all sequences

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| GTC (J99)     | DNA sequence obtained in-house.                              |

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